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CHEMICAL SCIENCES

A theoretical view on the stereochemistry of 1,3-benzoxazol-2-(3*H*)-ylidenes obtained from double vinylic substitution

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Abstract: 2-(1,3-Benzoxazol-2(3*H*)-ylidene)-3-oxo-3-phenylpropanenitrile (1) and methyl-2-(1,3-benzoxazol-2(3*H*)-ylidene)(cyano)acetate (2) are observed as single isomers by NMR spectroscopy. A theoretical study was carried out to investigate if this is due to the exclusive presence of the most stable diastereoisomer or if the ene moiety undergoes fast rotation, thereby allowing for the observation of an average conformer. Indeed, the pronounced stabilization of the E stereoisomer, attributed to intramolecular hydrogen bonding, makes it the single obtained product.

Key words: 1,3-benzoxazol-2-(3*H*)-ylidenes, Stereochemistry, Synthetic compounds, Theoretical view.

INTRODUCTION

Ketenedithioacetals have widespread use in organic chemistry, being important building blocks to obtain heterocyclic scaffolds using many different methods (Huang et al. 2020, Xu et al. 2019). Traditionally, these compounds are prepared by a one-pot reaction composed of: i) deprotonation of hydrogen active compounds, ii) addition to the carbon disulfide, and iii) methylation of the sulfide anions (Thomae et al. 2009).

Polarized ketenedithioacetals are substrates to vinylic substitutions, using diamines and aminols as nucleophiles to easily produce 1,3-diazo and 1,3-oxazo heterocycles of the imidazolidines, oxazolidines, hexahydropyrimidines, oxazinanes, and benzoxazole classes (Sangi et al. 2014, 2019).

Benzoxazoles play an important role in discovering novel agrochemicals of different classes, particularly herbicides (Zou et al. 2023), and are known for their large spectrum of pharmacological properties (Demmer & Bunch 2015), such as anticancer (Aboulwafa et al. 2023), antiviral (Wu et al. 2023) and antimicrobial activities (Padalkar et al. 2016); such properties are highly dependent on stereochemistry for an optimal enzyme induced-fit. Benzoxazole derivatives are usually synthesized by condensation between 2-aminophenols and carbonyl compounds; however, this method has limitations regarding their possible substituents (Sangi et al. 2014).

In our search for novel biologically active benzoxazoles, we synthesized 1,3-benzoxazol-2(3*H*)-ylidene-3-oxo-3-phenylpropanenitrile (1) and methyl-1,3-benzoxazol-2(3*H*)-ylidene(cyano) acetate (2) via double vinylic substitution of ketene dithioacetals, as shown in Figure 1, similarly to the synthetic route previously reported (Sangi et al. 2014, 2019, Bocion et al. 1977). However, it is uncertain whether the *E* stereoisomer is the exclusive product in solution due to the establishment of an NH...

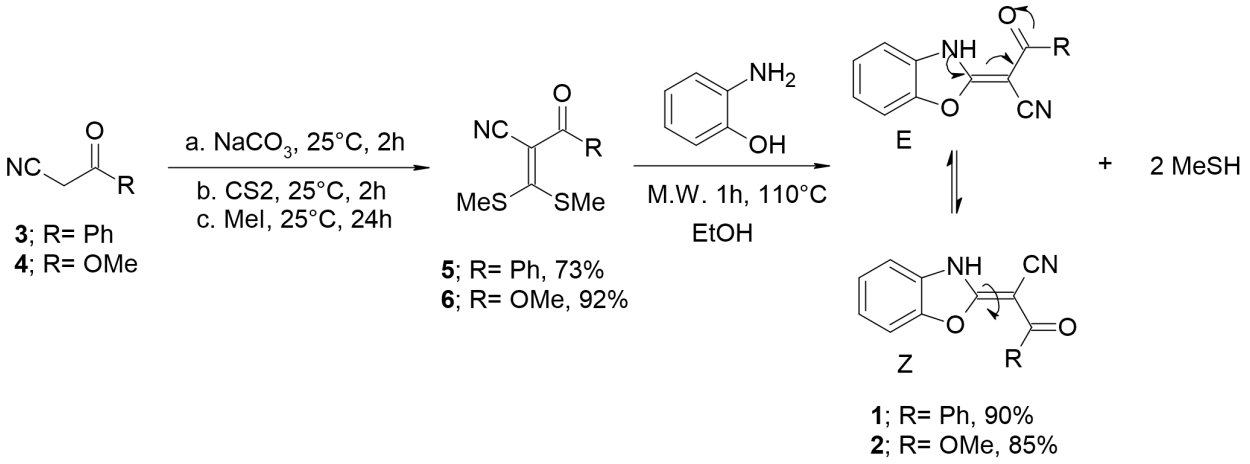

Figure 1. Synthetic route to obtain 1 (R = Ph) and 2 (R = OMe), which resonates allowing for conformational isomerization.

O=C intramolecular hydrogen bond, giving rise to a thermodynamic favored product, or if the ene moiety undergoes free rotation due to a resonance structure, allowing for conformational isomerization and the observation of an average conformation.

MATERIALS AND METHODS

General informations

All chemicals were purchased from commercial sources and used without any further Purification. 2-aminophenol, 2-benzoylacetonitrile, methyl 2-cyanoacetate, carbon disulfide and iodomethane were purchased from sigma aldrich, in pure form. The solvents N,N-dimethylformamide and ethanol were purchased AR grade from Dinâmica.

Reactions assisted by microwave irradiation were carried out in the device Anton Paar Monowave 300. Thin layer chromatography analyzes were performed on commercial aluminum plates with a 0.2 mm layer of silica in gel from the Macherey-Nagel brand, and visualizations were carried out under ultraviolet light (254 nm).

Infrared spectra were obtained using a spectrophotometer Bruker, FT-IR Vertex 70 model, using Attenuated Total Reflectance (ATR) mode, mass spectroscopy were performed in a Shimadzu GCMS-QP2010 Plus and NMR analyses were performed in a Bruker Avance DRX 300 and a Varian VNMRS 500MHz.

General procedure for the synthesis of ketene-dithioacetals

In a round-bottom flask, a mixture of a compound containing active hydrogen (benzoylacetonitrile (3), 20.6 g or methyl cyanoacetate (4), 17.6 mL) (0.2 mol), potassium carbonate (0.2 mol, 27.6 g), and dimethylformamide (240 mL) was prepared, stirring at room temperature for two hours.

Then, the reaction mixture was cooled to 0 °C, and carbon disulfide (0.2 mol, 12.1 mL) was added, keeping the resulting mixture under stirring at room temperature for two hours, with salt formation occurring.

Finally, methyl iodide (0.4 mol, 25.0 mL) was added, leaving the mixture at room temperature for twelve hours for alkylation of the sulfides to occur. After twelve hours, the reaction was completed with the addition of ice water (400 mL), leading to precipitation of the products.

The isolated products are obtained as solids after filtration and washing with water and had their purity qualitatively assessed by thin layer

chromatography before being sent for analysis by nuclear magnetic resonance.

The data from the nuclear magnetic resonance spectra of hydrogen (^{1}H NMR) and carbon (^{13}C NMR) that were used to identify the synthesized compounds are as follows.

2-Benzoyl-3,3-bis(methylsulfanyl) acrylonitrile (5): Yield 73%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91-7.87 (m, 2H); 7.57 (tt, *J* 7.2 and 1.5 Hz, ^{1}H); 7.49-7.44 (m, 2H); 2.77 (s, 3H); 2.49 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.3; 179.5; 136.6; 133.3; 129.1; 128.5; 117.6; 106.0; 20.2; 19.6.

Methyl 2-cyano-3,3-bis(methylsulfanyl) acrylate (6): Yield 92%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.76 (s, 3H); 2.68 (s, 3H); 2.53 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 181.6; 163.0; 116.3; 98.3; 77.4; 77.2; 77.0; 52.8; 21.2; 19.1.

General procedure for the synthesis of (1,3-Benzoxazol-2(3H)-ylidene) 1 and 2

In a glass suitable for microwave reactions, polarized dithioacetal (5, 0.249 g or 6, 0.203 g produced in the previous step) (1 mmol) and 2-aminophenol (1 mmol, 0.109 g) in ethanol (3 mL) were added. It was irradiated with microwaves for 60 minutes, maintaining a temperature at 110°C and constant stirring.

After completion of the reaction, the products described below were obtained in the form of precipitates that were isolated by simple filtration, with the products (1, 0.236 g and 2, 0.184 g) being obtained in pure form after washed with ethanol and water.

The data from the infrared spectroscopy, mass spectrometry and nuclear magnetic resonance spectra of hydrogen (^{1}H NMR) and carbon (^{13}C NMR) that were used to identify the synthesized compounds are as follows.

1,3-Benzoxazol-2(3*H*)-ylidene-3-oxo-3-phenylpropanenitrile (1): yield 90%. Melting point 210 - 212°C. IR (ATR) (ν/cm^{-1}): 3186 (ν N-H), 3058, 2205 (ν CN), 1609 (ν C=O), 1531, 1464, 1307, 1259, 734, 695. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.05 – 7.96 (m, 2H), 7.63 – 7.33 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 186.0 (C=O), 165.7 (C sp2 β CN), 146.9, 136.2, 132.2, 131.3, 128.4, 128.2, 126.1, 125.4, 116.8 (CN), 113.9, 111.4, 70.5 (C sp2 α CN). MS (m/z, (%)): 262 (M^{+}, 51); 261(71); 105(100); 77(99).

Methyl-1,3-benzoxazol-2(3*H*)-ylidene(cyano) acetate (2): yield 85%. Melting point: 267 - 272°C (decomposition). IR (ATR) (ν/cm^{-1}): 3288 (ν N-H), 2211 (ν CN), 1660 (ν C=O), 1566, 1443, 1384, 1297, 1229, 969, 756. ^{1}H NMR (300 MHz, DMSO-d^6) δ (ppm) 12.95 (s, 1H, N-H), 7.66 – 7.63 (m, 1H), 7.46 – 7.42 (m, 1H), 7.34 (dt, *J* 7.5 and 1.5 Hz, 1H), 7.30 – 7.24 (dt, *J* 7.5 and 1.5 Hz, 1H), 3,72 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, DMSO-d^6) δ (ppm) 166.3 (C=O), 165.7 (C sp2 β CN), 146.1, 130.6, 126.1, 124.5, 116.7 (CN), 113.0, 111.1, 56.3 (C sp2 α CN), 51.7 (OCH_3).

Computational Methods

The C=C rotational barriers in 1 and 2 were computed by scanning the N-C=C-C(=O) dihedral angle in steps of 10° using the density functional theory at the B3LYP/6-31g(d,p) level (Becke 1988, Lee et al. 1988, Ditchfield et al. 1971). The geometries of the energy minima were optimized at the B3LYP-D3(BJ)/DGTZVP level (Becke 1988, Godbout et al. 1992, Grimme et al. 2011), which includes empirical dispersion corrections, and no imaginary frequencies were found. The conformer/diastereoisomer stabilities were analyzed using a natural bond orbital (NBO) approach (Glendening et al. 2018). Calculations were all performed using the Gaussian 16 package of programs (Gaussian 16 et al. 2016).

RESULTS AND DISCUSSION

Considering that stereochemistry is a fundamental point to the mode of action with biological receptors, this work aims to understand why the *E* stereoisomer is the single product in solution, to give support to medicinal

and organic chemists to design potential drug candidates.

According to the DFT calculations, the rotational barriers of both 1 and 2 were computed as high as 20 (Z → E) to 35 (E → Z) kcal mol^{-1}, which prevents fast, free rotation at room temperature (Figure 1). For instance, the rotation time constants for ethane and butane are about 12 ps and 40 ps, respectively (Zheng et al. 2006). The C=C rotation barrier of typical alkenes is about 60 kcal mol^{-1}, while the corresponding value for the N-C(=O) bond of amides is 21 kcal mol^{-1} (Weil et al. 1967). A barrier of 20 kcal mol^{-1} corresponds to an interconversion rate of 1.3 × 10^{-2} s^{-1} at 25° C, that is, a half-life ($t_{1/2}$) of about 1 minute; $t_{1/2}$ for a barrier of 25 kcal mol^{-1} at 25° C is 66 hours (Eliel & Wilen 1994). Therefore, as the isomers of 1 and 2 could be separated at room temperature and analytically distinguished by NMR spectroscopy, only one form is produced, which is the thermodynamically most stable isomer *E*. It is worth mentioning that typical carbon-carbon single bonds have a length of 1.53 Å, while the corresponding value for double bonds is 1.34 Å (Robert & Caserio 1977); only the transition state of 1 and 2 upon rotation of the C=C bond approaches the carbon-carbon bond length of a single bond (≈ 1.43 Å). In contrast, the stable conformations have shorter carbon-carbon bond lengths of about 1.39 Å (Figure 2).

The *E* isomer is the single form observed experimentally because it is 8.1 and 6.2 kcal mol^{-1} more stable than the *Z* isomer (for 1 and 2, respectively), according to B3LYP-GD3(BJ)/DGTZVP calculations (Becke 1988, Godbout et al. 1992, Glendening et al. 2018) (Figure 3); because the transition state should experience similar interactions to the product, the thermodynamic product is likely the kinetic product too. To search for the interactions governing the "conformer" stabilities, a natural bond orbital analysis was carried out, and the Lewis and non-Lewis contributions to the overall electronic energies, as well as specific donor-acceptor interactions, were evaluated for both isomers. The second-order perturbation analysis of the donor-acceptor

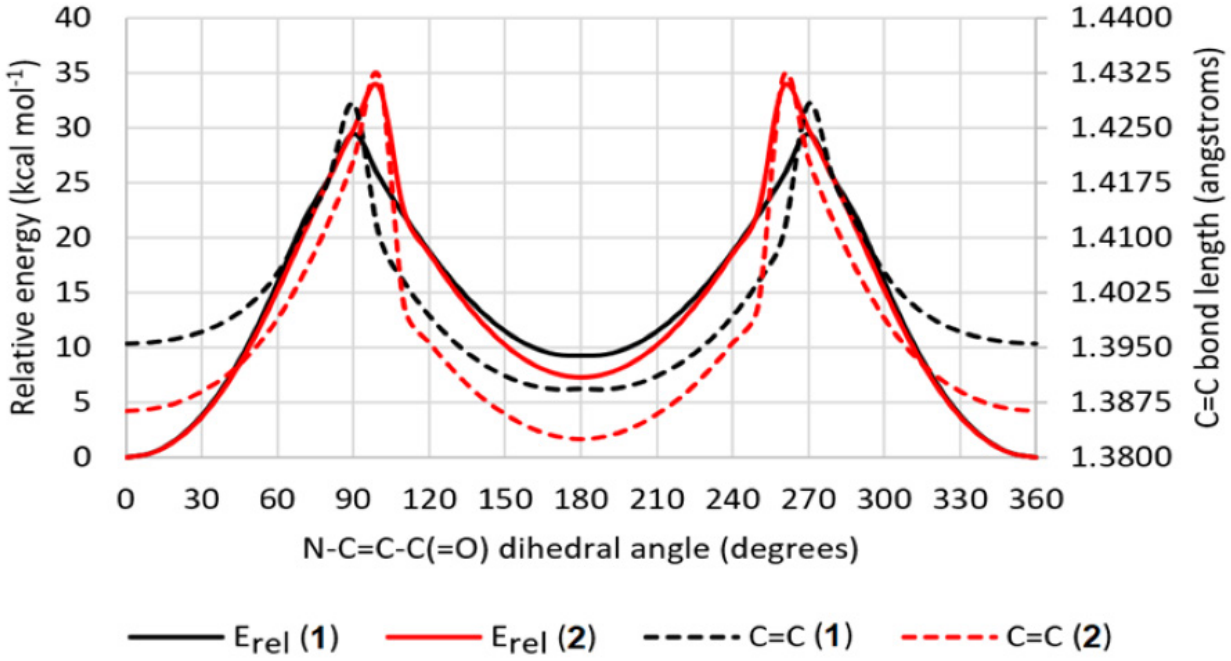

Figure 2. Angular dependence of the rotational electronic energy and C=C bond length in compounds 1 and 2 calculated at B3LYP/6-31g(d,p) level.

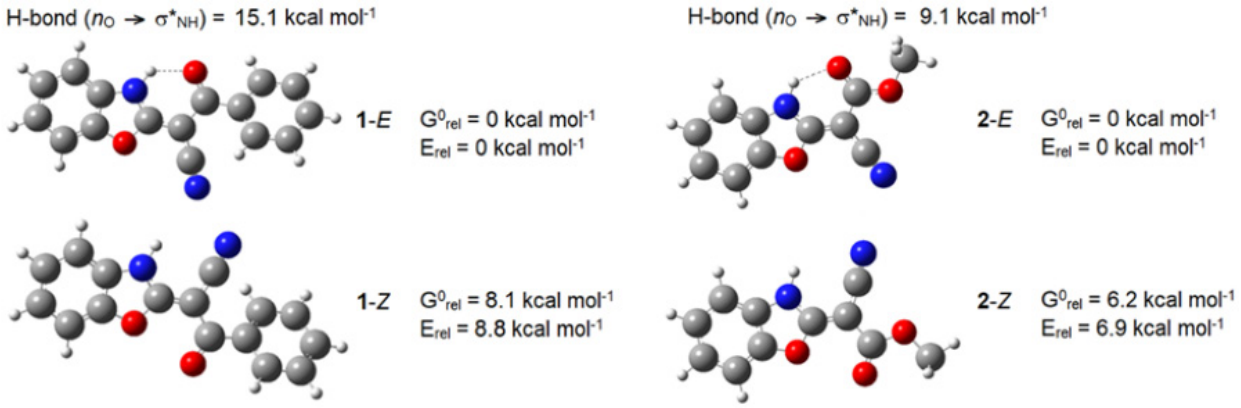

Figure 3. Stable "conformations" of 1 and 2, and the respective standard Gibbs free energies calculated at B3LYP-D3(BJ)/DGTZVP level.

interactions of the natural bond orbitals (NBOs) indicates that *E* is more sterically disfavored than *Z* (higher Lewis-type contributions), but much more stabilized by electron delocalization (non-Lewis contributions), particularly due to an $n_O \rightarrow \sigma^*_{NH}$ interaction (Figure 4) corresponding to a C=O···H–N intramolecular hydrogen bonding (IHB). A stabilizing (C=)O···O chalcogen bonding, such as the interaction governing the conformational isomerization of some systems containing the formamide and thiophene groups (Pascoe et al. 2017), does not appear to compete with the strong IHB since a corresponding $n_{(C=)O} \rightarrow \sigma^*_{O\text{-}C}$ electron delocalization is not effective, as shown in the NBO outcomes. This may be due to the formation of a five-membered ring, which is less favorable than a six-membered ring formed through the IHB.

CONCLUSIONS

The compounds 2-(1,3-Benzoxazol-2(3*H*)-ylidene)-3-oxo-3-phenylpropanenitrile (1) and methyl-2-(1,3-benzoxazol-2(3*H*)-ylidene) (cyano)acetate (2) are observed as single isomers by NMR spectroscopy. In this study, we carried out a theoretical study to show that the rotation barriers are high enough to prevent fast rotation, despite the presence of pseudo-double bonds, which often allow for isomerization. Consequently, the single isomer observed in the NMR spectra corresponds to the most stable diastereoisomer *E*, rather than an average structure that results from the diastereo isomerization in 1 and 2. This stability is attributed to the presence of an effective intramolecular hydrogen bonding, which stabilizes the *E* isomer, rather than a chalcogen bonding, which is absent in the *Z* isomer.

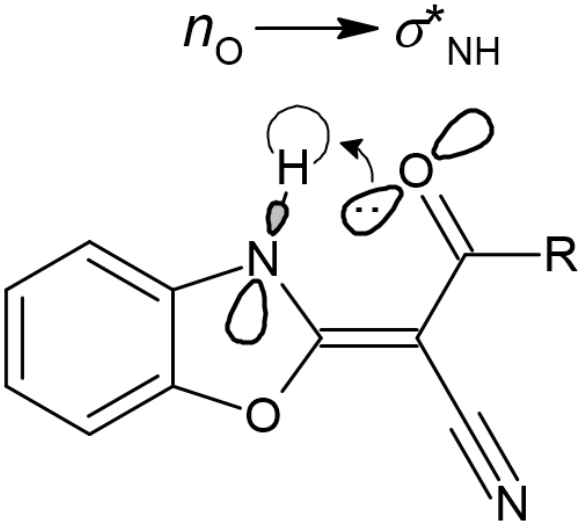

Figure 4. Quantum hydrogen bond in the E isomer of 1 (R = Ph) and 2 (R = OMe).

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